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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/820,656
Filing Date: April 08, 2004
Appellant(s): GONG ET AL.

Tamsen Valoir, Ph.D., Esq.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 3/20/2008 appealing from the Office action mailed 10/26/2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

WO 01/32144	Lechuga-Ballesteros ("Lechuga")	05-2001
6280729	Huang et al.	8-2001

Kurachi et al. "Biology of factor IX" Blood Coagulation and Fibrinolysis, 1993, vol. 4, pp 953-974.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.

3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

(A) Claims 29, 33, 37, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lechuga-Ballesteros et al. (WO 01/32144) ("Lechuga") in view of Kurachi et al. (Blood Coagulation and Fibrinolysis, 1993; ("Kurachi")).

Appellant Claims

Appellants claim (1) a method of preventing hemophilic bleeding in advance of a bleeding event comprising (a) aerosolizing monomeric Factor IX (FIX) wherein the aerosolized FIX: (i) has a mass median aerodynamic diameter of between 2-4 microns, (ii) a fine particle fraction percent less than 3.3 microns of at least 50%, (iii) is at least 90% monomeric, (iv) having after-aerosolization activity/pre-aerosolization activity of at least 80%, and (v) is a dry powder having less than 10% water w/w, but does not have ethanol; (b) slowly maximally inhaling aerosolized monomeric FIX; (c) allowing said monomeric FIX to deposit in the deep lung tissue

such that said monomeric FIX is sequestered in said deep lung tissue to provide sufficient FIX to prevent bleeding for at least 100 hours after administration.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Lechuga discloses dry powder compositions having improved dispersivity comprising an active agent and a dipeptide or tripeptide comprising at least two leucyl residues. These compositions exhibit superior aerosol properties and are preferred for aerosolized administration to the lung (title and abstract).

Lechuga discloses that the active agent may be an inorganic or an organic compound, including drugs, which act on systems, including the blood circulatory system (pg. 9, lines 12-13 and 16). Specific drugs include Factor VIII or Factor IX (pg. 10, line 8). Example 7, beginning on page 44, specifically describes Factor IX dry powder formulations comprising buffer (i.e. Na Citrate) and trileucine (see Table 15, for example).

Lechuga discloses that exemplary peptide trimers include leu-leu-leu (i.e. tri-leucine) and that preferred peptides include dileucine and trileucine (page 13, lines 5 and 10).

Lechuga discloses that the addition of trileucine to a calcitonin formulation was effective to nearly double the ED value (emitted dose value) of the resulting powder (Example 4).

Lechuga discloses that the dry powders are preferably prepared by spray drying and active agents having a water solubility of at least about 0.10 mg/ml can be spray dried from aqueous solution (pg. 17, lines 7 and 12-14). Where the active agent is hydrophobic, it can be dissolved in an organic solvent or co-solvent system, the hydrophilic components (e.g. leucyl-containing peptides and optional excipients) are at least partially dissolved in the same cosolvent

system, and the resulting solution is spray dried. Dry powders may also be prepared by combining aqueous solutions or suspensions of formulation components and spray drying simultaneously in a spray dryer (pg. 18, lines 4-10 and 24-26).

Lechuga discloses that the compositions may additionally comprise one or more pharmaceutical excipients suitable for pulmonary administration in amounts ranging from 0.01% to about 95% by weight (pg. 14, lines 24-28). The compositions may also include a buffer or a pH-adjusting agent, wherein representative buffers include organic acid salts (pg 16, lines 5-9). The compositions may be in powdered form or may be flowable liquids (pg. 16, lines 29-30). The dry powder particles have a mass median diameter (MMD) of less than about 20 microns, most preferably less than about 4 microns and usually in the range of 0.1 microns to 5 microns in diameter. The powder particles also have a mass medium aerodynamic diameter (MMAD) less than about 10 microns, most preferably between 1.5 to 3.5 microns. These powders generally have moisture content below 20%, usually below 10%, and preferably below 6%. Such low moisture-containing solids tend to exhibit a greater stability upon packaging and storage (pg. 20, lines 3-7, 12-17, and 26-29).

Lechuga discloses that the compositions generally have emitted doses (ED) usually greater than 40%, and often greater than 55%. The incorporation of di-leucyl or tripeptide into a variety of active agent formulations was effective, in all cases, to increase the ED value of the resultant compositions, and in some cases doubling the ED value (pg. 21, lines 1-8; See also Table 9 on page 38). Tri-leucine was more effective in enhancing powder dispersibility than leucine (pg. 39, lines 8-9).

Lechuga discloses that the dry powder compositions are also characterized by a fine particle dose or fraction (FPD or FPF), which describes the percentage of powder having an aerodynamic diameter less than 3.3 micron. The powder compositions of Lechuga's invention possess FPF values ranging from about 35% to 85%, and are thus extremely effective in reaching the regions of the lung, including the alveoli (pg. 21, lines 10-17).

Lechuga discloses that the formulations of his invention may be delivered using any suitable dry powder inhaler (DPI), an inhaler device utilizing the patient's inhaled breath as a vehicle to transport the dry powder drug to the lungs. When administered with a DPI, the powder is contained in a receptacle having a puncturable lid or other access surface, preferably a blister package or cartridge, where the receptacle may contain a single dosage unit or multiple dosage units (pg. 22, lines 20-23 and 27-30).

Lechuga discloses that the compositions of his invention are useful when administered pulmonarily in a therapeutically effective amount to a mammalian subject for treating or preventing any condition responsive to the administration of an active agent (e.g. hemophilia treated with Factor IX) (pg. 24, lines 10-13).

It is art recognized that biologically active factor IX is monomeric (i.e. it is comprised of a single polypeptide chain), as evidenced by the literature review of Kurachi, K. et al. ("Biology of Factor IX," *Blood Coagulation and Fibrinolysis*, **1993**, *4*, 953-974), wherein it is taught that "…mature plasma factor IX is a single polypeptide chain..." (pg. 954, right hand column, 2nd paragraph and Figure 2 on pg. 955).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Lechuga does not explicitly teach or disclose anticipatory methods of treating hemophilia, preventing bleeding associated with a hemophilic assault as stated in the instant claims, specify the treatment of hemophilia B, teach monomeric percentage of FIX, the step of "slowly maximally inhaling", or the "step" of " allowing said monomeric FIX to deposit in the deep lung tissue." These deficiencies are obviated by the teachings of Lechuga or are obviated per the teachings of Kurachi.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention that Lechuga implicitly teaches methods of treating hemophilia by administration of Factor IX, because Factor IX is a well-known active agent used in the treatment of Hemophilia B (See for example Lacy, C.; Armstrong, L. L.; Lipsy, R. J.; Lance, L. L. *Drug Information Handbook*, Lexi-Comp, Inc.: Cleveland, **1993**, pp 363-364.) and is one of the active agents that Lechuga teaches may be delivered using any suitable dry powder inhaler (DPI), an inhaler device utilizing the patient's inhaled breath as a vehicle to transport the dry powder drug to the lungs. It would have been apparent to a skilled artisan that the use of a DPI (i.e. a Dry Powder Inhaler) to deliver Lechuga's compositions results in the aerosolization of the powder formulation and entails the step of inhalation. The step of exhalation would have been obvious to a person of ordinary skill in the art at the time of the instant application, because every inhalation by a living respiring subject is followed by an exhalation, as evidenced by observing one's own breathing. Therefore, the steps of the method of treating hemophilia as

claimed by the Appellants are conventional steps and/or are obvious over the teachings of the prior art.

Regarding the stated method of preventing hemophilic bleeding in advance of a hemophilic assault, because the composition taught by Lechuga has the same components as that claimed by Appellants and the treatment of the hemophilia is a consequence of the delivery of the active composition by inhalation and ordinary skilled artisan would have arrived at the claimed method upon taking the inhalable FIX dry powders prepared by Lechuga onto the next logical step of administering said powder to a hemophiliac to test the effectiveness of said powder in the treatment of hemophilic bleeding. Regarding the required absence of ethanol in the formulations, the Examiner contends that the term "dry" implies the absence of liquid (i.e. solvent, such as alcohol). Furthermore, Lechuga teaches that the dry powders may be prepared by spray drying aqueous solutions. The word "aqueous" does not imply or require the presence of alcohol (i.e. ethanol). Thus, it is concluded that the inhalable FIX dry powders invented by Lechuga are prepared in from aqueous solutions that do not require the presence of ethanol.

(B) Claims 32 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lechuga in view of Kurachi as applied to claims 29, 33, 37, and 40 above, and further in view of Huang et al. (U.S. Patent No. 6,280,729; "Huang").

Appellant Claims

Appellants claim a method of preventing hemophilic bleeding in advance of a bleeding event comprising as described wherein the method utilizes FIX prepared by (A) diafiltering

concentrated FIX solution to a concentration of approximately 12 mg/ml; (B) spray drying the diafiltered solution at 40 or 60 psi and 60°C or 70°C at 5 ml/min and 17.8 standard cubic feet per minute (scfm); and (C) transferring spray dried FIX to a sealed storage container at less than 5% relative humidity.

NOTE: Contrary to Appellants' assertions, Appellants claims do not recite spray drying a diafiltered solution at a range of 40-60 psi and a temperature range of 60-70°C.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Lechuga and Kurachi were set forth above.

Huang teaches the preparation of Factor IX (title; abstract; col. 3, lines 45-55; col. 8, line 33 through col. 11, line 43). Specifically, Huang teaches that according to the prior art it is known and desirable to remove salt from FIX solutions to obtain a solution that is osmotically compatible with human tissues and this salt removal is routinely achieved via ultrafiltration and diafiltration (col. 4, lines 5-14 and 43-48; col. 9, lines 46-56; col. 10, lines 16-49). The routine nature of diafiltration of FIX solutions is especially evident in the below text:

> Typically, the bound factor IX is washed, and then eluted from the anion exchange resin using a buffered salt solution of high molarity. Inasmuch as such high molarity salt solution is considered osmotically incompatible with human tissues, practitioners of the prior art invariably subject their factor IX extracts to dialysis and filtration (or alternately ultrafiltration and diafiltration) which place the factor IX extract in concentrated form, but replace the high molarity salt solution with a physiologically-compatible low molarity salt solution.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Lechuga and Kurachi lack the teaching of diafiltration. This deficiency is cured by the teachings of Huang.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to modify the teachings of Lechuga and Kurachi to diafilter solutions of FIX prior to spray drying, because it is undesirable to administer composition that are osmotically incompatible with human tissues. An ordinary skilled artisan would have been motivated to diafilter a FIX solution; because in the routine purification of FIX one obtains high molarity buffered salt solutions and said salt solutions are osmotically incompatible with human tissues. Furthermore, an ordinary skilled artisan would have been motivated to diafilter a FIX solution, because this is a conventional step used in the purification of FIX solutions. Regarding the other steps in making the FIX dry powders utilized in the claimed methods, the prior art teaches spray drying (see Lechuga) and Appellants have not demonstrated the criticality of spray drying at a pressure of approximately 50 psi between a temperature of 60 °C and 70 °C at a rate of 5 ml/min and approximately 18 scfm. Regarding the step of transferring FIX to a sealed container at less than 5% humidity, the prior art teaches that the dry powder formulations are preferably maintained under dry (i.e. relatively low humidity) conditions during manufacture, processing, and storage (Lechuga, pg. 19, lines 18-20). A humidity of less than 5% reads on "relatively low humidity conditions." Notwithstanding this, Appellants have not demonstrated the criticality of

the transfer step occurring under an atmosphere having humidity of 5% or less. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

(10) Response to Argument

Rejection (A)

Appellants have traversed rejection (A), restated above for Appellants' and the Board's convenience, based on the following implicit/explicit arguments: (i) the cited art allegedly does not teach or suggest all the claimed limitations; (ii) the cited prior art references are allegedly explicitly or implicitly missing the following elements: (a) preventing hemophilic bleeding in advance of a bleeding event, (b) at least 90% monomeric after-aerosolization, (c) 80% activity retained after aerosolization, (d) does not have ethanol, (e) slowly maximally inhaling; (iii) in Appellants' opinion the teachings of Kurachi are allegedly irrelevant; (iv) the prior art formulations are not identical and thus the recited elements are allegedly missing; (v) Appellants believe inherency is relied upon to rely seven missing elements; (vi) the properties that Appellants believe are argued by the Office as being inherent are allegedly not necessarily present; (vii) in Appellants' opinion the Office has allegedly based its arguments and conclusions on allegedly unreasonable assumptions; (viii) there is allegedly no expectation of success; (ix) the Office has allegedly improperly shifted burden to Appellants; (x) the Office has allegedly failed to provide "competent evidence" under declaration as Appellants mistakenly believe is required; (xi) the prior art treatments teach away from Appellants' claimed invention; (xii)

Appellants' observation of a sequestration effect is allegedly sufficient to show unobviousness when compared to intravenous administration of FIX; (xiii) the Office allegedly dismisses Appellants' perceived "head-to-head data"; and (xiv) Appellants' reliance on the teachings of Gupta concerning intravenous bolus administration of liquid FIX compositions and the teachings of others concerning aerosolized liquid protein formulations allegedly provide "competent evidence" in support of Appellants' arguments.

The Examiner respectfully disagrees with Appellants' arguments for the reasons stated on the record and further articulated herein below. Regarding (i), this argument will necessarily be addressed with the remaining arguments. Regarding (ii), Appellants are correct that the cited combined prior art does not explicitly teach (a) preventing hemophilic bleeding, (b) FIX that is at least 90% monomeric after aerosolization and that maintains 80% activity after aerosolization, or (c) slowly, maximally inhaling. However, Appellants have misread the cited prior art as teaching FIX formulations that necessarily comprise ethanol and Appellants provided no objective evidence that Lechuga's formulations necessarily contain ethanol. In fact, it is noted that Lechuga teaches that Example 2 (pg. 33, line 20 through pg. 34 line 20) is illustrative of the preparation of inhalable dry powders comprising an active protein in combination with either leucine or tri-leucine and that the inhalable FIX dry powder preparations were made as described previously in Lechuga's WO document (see Example 7: page 44, lines 15-19). Lechuga's preparation of said inhalable dry powders comprising active protein does not utilize ethanol, but rather aqueous solutions with a total solids content of 1% w/v. Although Lechuga does indicate in section IV on page 17 that the aqueous formulations may optionally contain additional water-

miscible solvents, such as acetone, alcohols, and the like, these solvents are not required by Lechuga's method as evidence by the illustrative procedure of Lechuga's Example 2.

Concerning the step of "slowly, maximally inhaling", Appellants argued in their after final remarks submitted on December 12, 2007 that the phrase "slowly, maximally inhaling" is a term of art with an accepted meaning; and that "Many researches in the field of inhalation therapy have used the exact phrase "slow maximal inhalation" or the similar phrase "slow deep inhalation" as evidenced by Appellants' citation of five references, including instructions from the NIH. Appellants cannot have their cake and eat it too and simultaneously argue that the phrase "slowly, maximally inhaling" is both an art-recognized term with an accepted meaning and conventionally known, as evidenced by the use of this term by "Many researchers in the field". Thus, one can only conclude per Appellants' arguments in their after final remarks submitted on December 12, 2007 that the phrase "slowly, maximally inhaling" is both art-recognized, well-known, and conventional in the inhalation administration of pharmaceutical formulations.

Concerning the recitation that the aerosolized FIX is 90% monomeric, Appellants' specification (See Tables 3b and 7b on pages 14 and 20, respectively, and paragraph 83 on page 21), indicates that only inhalable spray dried FIX powders made from pre-spray-dried aqueous formulations comprising 0.05% ethanol (i.e. lot 4) exhibited a FIX monomer content of less than 90% after two weeks of storage at 40 °C/75% relative humidity (RH), whereas the lot 4 sample exhibited a FIX monomer content of greater than 90% after two weeks of storage under all other conditions tested. Contrary to Appellants' opinion, the native active form of FIX, as taught by Kurachi as being a single polypeptide (i.e. monomeric), is relevant, because it sets forth what is

the naturally produced form of FIX; and as Appellants are well aware, in nature, structure often dictates function. It is also noted that Appellants have cited references suggesting that the presence of ethanol results in protein aggregation (i.e. a decrease in protein monomer content) (See, for example, the citation of Choi et al. on page 17, footnote 14 of Appellants' brief). Thus, it is reasonably concluded that Lechuga's inhalable FIX dry powder formulations made from spray dried aqueous formulations not containing ethanol would exhibit a monomer content in excess of 90% after aerosolization. Similarly, it is a reasonable conclusion that Lechuga's inhalable FIX dry powder formulations also would necessarily exhibit the same or substantially similar after-aerosolization activity, because Lechuga's formulations are made from spray-dried aqueous preparations that do not contain ethanol.

Regarding (iii) Appellants have provided no specific objective evidence that the *in vivo* structure of FIX is not relevant to the issues at hand. Rather Appellants have made generalizations, implying that most if not all proteins are expected to clump and deteriorate upon drying and subsequent aerosolization. In fact, Appellants' generalizations are not credible, as evidenced by the data provided by Lechuga that aerosolization of Lechuga's invented inhalable dry powder FIX preparations is characterized by an MMAD of 2.7 microns and an emitted dose of 89% (Example 7; pg. 44, Table 15, lines 20-28). Clearly, if Lechuga's invented compositions were as plagued by the problems of clumping/deterioration as implied by Appellants' generalizations, than Lechuga would not have obtained dry powders characterized by such a high emitted dose of fine (i.e. unclumped and unaggregated) particles as is clearly and irrefutably demonstrated in Lechuga's Table 15 on page 44.

The gist of Appellants' argument (iv) is that because the inhalable FIX dry powder formulations invented by Lechuga are not identical (i.e. anticipatory) to Appellants' invented and tested formulations that Appellants' claimed method of administering a FIX dry powder to treat hemophilic bleeding, for which FIX is art-recognized as being suitable, is unobvious. This argument is unpersuasive, because the pending claims are properly rejected under 35 USC §103(a) and not 35 USC §102. Thus, it is permissible for the prior art formulations to not be identical with the formulations administered in Appellants' exemplified methods. Regarding the recitation of Appellants' observation of a sequestration and dosing effect, the Lechuga formulation contains (i) the same active agent as Appellants administer in their claimed method, (ii) is in the same form (i.e. an inhalable dry powder), (iii) with the required MMAD (i.e. an MMAD of 2.7 microns is within the required MMAD range of 2-4 microns), and (iv) an overlapping required FPF (i.e. Lechuga teaches that the powders have a FPF of 35%-85%) and, thus, would reasonably be expected to exhibit similar properties. Administration of Lechuga's invented inhalable FIX dry powders necessarily will deposit in the deep lung tissue, because Lechuga's powders have the same MMAD as the powders administered in Appellants' method.

Regarding (v)-(vi), Appellants believe that inherency is being relied upon to address the following limitations: (a) ethanol is not present in the aerosolized FIX dry powder, (b) a FIX monomer content of 90% or more, (c) a FPF less than 3.3 microns of at least 50%, (d) post-aerosolization activity of at least 80%, (e) water content less than 10% w/w, (f) prevention of hemophilic bleeding in advance of an event, and (g) sufficient FIX to prevent bleeding for at least 100 hours after administration. Appellants are mistaken in their beliefs concerning the Office's alleged inherency arguments. As was stated above, the Office is not arguing that the

formulations inherently do not contain ethanol, but rather that Lechuga teaches invented inhalable FIX dry powder formulations that are made from aqueous formulations in which ethanol is an optional component that is not required. The Office's position regarding the required 90%+ FIX monomer content and 80%+ post-aerosolization activity, as stated above, is that because the inhalable FIX dry powder formulations invented by Lechuga are made from fine, unagglomerated, unaggregated spray dried aqueous formulations, as evidenced by the high emitted dose and MMAD of 2.7 microns and FIX exists as a single polypeptide in vivo, it is a reasonable conclusion that Lechuga's invented inhalable FIX dry powder formulations would have a greater than 90% FIX monomer content and 80% post-aerosolization activity. Concerning FPF, Lechuga clearly teaches that the invented powders comprising an active protein have a FPF that overlaps significantly with the FPF required by Appellants' claims, and thus obviates the claimed FPF. Furthermore, conventional practice in the development of inhalable pharmaceutical preparations recognizes that FPF is a result effective parameter that one would routinely optimize. Concerning the required water content, Lechuga clearly directs the ordinary skilled artisan to obtain inhalable dry powders having a water content less than 10% and preferably below 6% (pg. 20, lines 3-7, 12-17, and 26-29). This teaching provides ample suggestion and motivation to the ordinary skilled artisan to minimize water content. Finally concerning the observed sequestration effect and the claimed prophylactic property, administration of Lechuga's invented inhalable FIX dry powder formulations would reasonably be expected to exhibit the same or substantially similar properties, because Lechuga's invented inhalable FIX dry powder formulations comprise the same active agent, exhibit the required MMAD, preferably have a water content below 6% (i.e. this meets the limitation of a water

content less than 10%), and have a FPF that overlaps significantly with the FPF required by Appellants' method (i.e. Lechuga teaches a FPF of 35-85% and Appellants' claims require a FPF of less than 3.3 microns of 50-100%).

Regarding (vii)-(ix), Appellants' have based these arguments upon a misreading of Gupta, which has not been relied upon to reject Appellants claims, and erroneous conclusions therefrom. Specifically, Appellants cite from Gupta a statement that dehydration and subsequent comminution of proteins may lead to loss of activity. Comminution is grinding or milling. Lechuga does not teach that the invented inhalable FIX dry powder formulations are prepared by grinding or milling, but rather by spray-drying aqueous formulations, which is the same method Appellants use to prepare their invented FIX formulations. Furthermore, although Gupta indicates that jet nebulization may result in shearing forces that could denature protein (paragraph bridging pages 429-430), Gupta also teaches that presence of surface-active BSA (bovine serum albumin) protects FIX from shear-induced denaturation. The Board's and Appellants' attention are directed to Lechuga's Example 1 (pg. 26-33, especially pg. 33, lines 1-19), which clearly demonstrates that the tri-leucine present in Lechuga's invented inhalable FIX dry powder formulations is surface active. Lowering the surface tension of water is a measure of a compounds' surface activity. The amount of trileucine present in Lechuga's exemplified inhalable FIX dry powder formulations (See Example 7, pg. 44, Table 15 in Lechuga) is the same amount present in the FIX formulations tested by Appellants (see section F on pg. 14 of Appellants' brief). Therefore, both the prior art's and Appellants' pre-spray dried liquid formulations comprise the same amounts of the same surface active agent (i.e. trileucine), which per the teachings of Gupta would be expected to protect dissolved FIX from shear-induced

denaturation. Thus, Appellants' conclusion that Lechuga's invented inhalable FIX dry powder formulations would necessarily comprise denatured FIX in the form of "clumped" dry powder is erroneous. Finally, Appellants' generalizations and statements regarding "expected clumping, allegedly per the teachings of Appellants' cited prior art, have been refuted above, as evidenced by the fact that Lechuga's invented and exemplified inhalable FIX dry powder formulations are characterized by a very high emitted dose of fine particles with an MMAD of 2.7 microns and an ordinary skilled artisan would indeed have a reasonable expectation of success.

Concerning (ix), the office has properly demonstrated a *prima facie* case of obviousness and shifted the burden to Appellants to demonstrate with objective evidence, such as by a direct side-by-side comparison with Lechuga's invented inhalable FIX dry powder formulations and Appellants' invented formulations, that Lechuga's invented inhalable FIX dry powder formulations undergo clumping.

Concerning (x), the Examiner agrees that it is impermissible to base findings of obviousness upon his own expertise. Thankfully, the substantial competent evidence of record that has clearly been set forth by the teachings of the combined prior art references of Lechuga and Kurachi clearly set forth a proper *prima facie* case of obviousness as articulated repeatedly on the record and herein above. Furthermore, it is noted that in the course of the examination of the instant application, the Office has never relied on official notice, but rather on the explicit and implicit teachings of the cited prior art and reasonable logical conclusions, as it is proper to do and is supported by the courts (KSR Intl. Col. V. Teleflex Inc. 127 S. Ct. 1727, 1742, 82 USPQ2d 1385, 1398 (2007)).

Regarding (xi), Appellants assert that Gupta, which teaches the intravenous bolus administration of FIX liquid formulations, is the closest prior art. Appellants are wrong. The closest prior art is Lechuga, which teaches inhalable FIX dry powder formulations, because Appellants administer inhalable dry powder FIX formulations and do not administer FIX by intravenous administration. Common sense, which the Supreme Court has held can also be used to show obviousness (KSR Intl. Col. V. Teleflex Inc. 127 S. Ct. 1727, 1742, 82 USPQ2d 1385, 1398 (2007)), indicates that an inhalable dry powder is suitable for inhalation (i.e. aerosolization). Thus, Lechuga's teachings implicitly include the suggestion to administer Lechuga's invented inhalable FIX dry powder formulations by inhalation and cannot be construed as a teaching away from Appellants' claimed invention.

Regarding (xii)-(xiii), Appellants have not provided competent "head-to-head data", because Lechuga, not Gupta, is the closest prior art. Furthermore, due to the substantial similarities between Lechuga's invented and exemplified inhalable FIX dry powder formulations and the FIX formulation administered in Appellants' methods, it is reasonable to conclude that one would observe the same or similar sequestration and dosing effects as observed by Appellants. In conclusion, for the aforementioned reasons stated herein and stated repeatedly on the record, it is respectfully concluded that the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the invention claimed in claims 29, 33, 37, and 40 of the instant application.

Rejection (B)

Appellants have traversed rejection (B), restated above for Appellants' and the Board's convenience, based on the same implicit/explicit arguments presented in traversal of rejection (A). The rebuttal of these arguments is herein incorporated by reference. Appellants have also traversed the instant rejection by arguing that Huang allegedly teaches away from Appellants' claimed invention, because Huang allegedly teaches away from the routine use of diafiltration as a conventional step in the purification of FIX, as allegedly evidence by Example 2, Table 1 of Huang.

The Examiner respectfully disagrees with Appellants' traversal arguments for the reasons stated above herein and, regarding the allegation that the Huang reference teaches away, this argument is rebutted herein below.

Appellants have misread the teachings of Huang and incorrectly concluded that Huang teaches away from the routine use of diafiltration. Rather Huang teaches the use of high molarity salts for the long-term storage of FIX in solution, or until impurities known to contribute to FIX degradation (col. 10, lines 26-37), such as, proteases present in an intermediate prothrombin complex concentrate (see Col. 8, line 66 through col. 9, line 8), are removed. Huang also teaches that after removal of the proteolytic impurities is accomplished, if desired the high salt concentration can be reduced (col. 10, lines 38-49), such as would occur during diafiltration. For example, in Huang's Example 1 (col. 16, line 50 through col. 18, line 35), which describes a methodology to obtain an "improved factor IX final product", Huang indicates that the final purification steps include diafiltration, clarification, and sterile filtration (col. 18, lines 28-35). Furthermore, it is noted that the Lechuga reference does not teach inhalable FIX

dry powder formulations made from aqueous FIX formulations that have been stored for a long time or that the inhalable FIX dry powder formulations are converted into solutions or suspensions for long-term storage. Additionally, one would not reasonably expect FIX present in a dry powder to undergo degradation processes that occur in solution. In conclusion, Huang does not teach against the use of diafiltration as a conventional purification technique, but rather teaches additional purification steps that when combined with diafiltration minimize solution degradation of FIX during long-term storage in solution and an ordinary skilled artisan would have been motivated to utilize diafiltration to purify FIX solutions prior to spray drying to obtain inhalable FIX dry powder formulations. The instant rejection remains proper.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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